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Determining Predictors of Response to Ambulatory Pharmacist-led Diabetes Care

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Determining Predictors of Response to Ambulatory Pharmacist-led Diabetes Care

by

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Dedication

I dedicate this project to multiple people who were essential in making this a reality. First, to my mother who taught me the importance of patience and hard work. Without you, I would not have made it this far or persisted this long. Second, to my brother Troy. You have always inspired me to value education and reach my goals. Thank you for paving the way and for being a true role model for me. Next, to my close friends who were my emotional support and motivation throughout this journey. I would also like to dedicate this to my late brother-in-law, Kip Carpenter, who we lost in July 2019. I will never forget you, the lessons you taught me, or the impact you had on my life. This is for Kip and the many people around us who are battling chronic metabolic diseases. Lastly, I dedicate this thesis to the many patients who sought pharmacist care and ultimately allowed for this data to be captured. It is my hope to use these results to further improve access to quality health care in the United States.

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Abstract

Determining Predictors of Response to Ambulatory Pharmacist-led Diabetes Care

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Purpose: There is a lack of guidance in referring patients to the clinical pharmacist for diabetes management, which likely results in patients missing out on this beneficial service. It would be useful to know which patients and specific clinical interventions are most likely to show benefit from pharmacy services. To our knowledge, only one study has assessed patient predictors of response to diabetes care provided by a clinical pharmacist, which was limited to baseline variables. Therefore, the primary objective was to describe clinical responses to pharmacist-led diabetes care and to identify baseline and interventional variables that are independently predictive of clinical response.

Methods: This was a retrospective cohort study using patient data from two health systems in San Antonio, Texas. Included patients were ≥18 years old with a referral to the pharmacist for Type 2 Diabetes management. Patients were followed for up to 6 months and data were collected at baseline, during follow-up, and at the end of the study. Clinical response was defined as a reduction in the A1C from baseline by ≥1% or meeting the documented A1C goal. Non-

responders failed to meet these A1C goals. Variables with P<0.20 on bivariate analysis were included in the multiple variable logistic regression model to determine predictors of response.

Results: A total of 180 patients were included. Overall, patients were predominantly female (63%) and obese (58%) with a disease duration ≥10 years (67%). The median (IQR) change in A1C from baseline for responders and non-responders was -2.2% (-3.7 to 1.3) and 0.4% (-0.4 to 1.05) (P<0.001), respectively. Sixty-six percent of patients were considered responders. Significant predictors of response included baseline A1C (OR 1.41; 95% CI 1.08-1.85), number of completed visits with both the physician (OR 0.69; 95% CI 0.49-0.96) and the pharmacist (OR 1.65; 95% CI 1.03-2.64), and medication optimization (OR 10.7; 95% CI 1.04-109.9).

Conclusion: Pharmacists are effective in diabetes management. Specifically, more visits with the pharmacist and utilizing medication optimization are especially helpful in lowering the A1C. Higher baseline A1C values are also predictive of response and should be incorporated into new protocols for pharmacist management of diabetes.

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Chapter One: Current Healthcare Landscape in the United States

Chronic Disease Burden and Population Challenges

Chronic diseases are highly prevalent in the United States (U.S.) today. A chronic disease is one that lasts one year or more, limits functional capacity, and requires ongoing medical treatment.[1] Common examples include cancer, heart disease, diabetes mellitus, and chronic kidney disease. In 2014, 6 in 10 Americans had at least one chronic disease and 4 in 10 had more than one.[1] In fact, the leading causes of death in the U.S. in 2017 were heart disease and cancer with 647,457 and 599,108 deaths, respectively.[2] Notably, diabetes mellitus as a cause of death has more than doubled from 34,583 deaths in 1980 to 83,564 deaths in 2017.[3] Multiple chronic diseases contribute to increased healthcare burden and resource utilization. For example, patients with five or more conditions spend about 14 times more on healthcare expenditures per year compared to patients with no chronic diseases. This includes prescription medications, hospital stays, and emergency room visits, among other costs. With a significant portion of the population affected and many healthcare dollars spent on chronic diseases, more emphasis should be placed on their management and prevention.

Chronic diseases disproportionately affect older adults. The proportion of multiple chronic conditions in those 65 years and older (81%) is substantially higher compared to those 45-64 years (50%) and 18-44 years (18%).[1,4,5] Thus, an aging population exacerbates the high burden of chronic disease on the U.S. healthcare system. Adults ≥65 years old are expected to more than double in population from 46 million to 98 million by 2060.[6] In comparison, the population <18 years old is only expected to grow 3% during the same timeframe. This growth will likely lead to increased utilization of healthcare resources, as well as place a strain on the

resources that support this population. The elderly support ratio, which is the number of working-age adults (18-64 years old) for every person ≥65 years old, will continue to decrease by 2060.[6] Historically, it has decreased from 6.0 in 1960 to 5.0 in 2000 and ultimately to 4.3 in 2014. By 2030, the elderly support ratio is expected to dip to 2.8 and to 2.4 by 2060. This decrease illustrates declining resources to care for an aging population and highlights the need for more resources in primary care.

EVOLVING PRIMARY CARE IN THE UNITED STATES

Primary care describes comprehensive healthcare delivery in the outpatient setting and serves as a main way that patients access and receive medical care. In fact, it is often the first interaction many patients have with the medical system. With focus on overall health and wellness, it is essential in maintaining continuity of care. Primary care is an ideal setting to manage most chronic disease conditions faced today because of the need for persistent attention and follow-up. Primary healthcare delivery in the U.S. is constantly evolving. In particular, team-based care is increasingly common given patient health complexities and requirements. Healthcare teams are interprofessional and essential in order to alleviate workload from one provider and to deliver high-quality health care in today's demanding society. At the same time, healthcare delivery has shifted to value-based care which emphasizes cost savings and quality.[7] The Patient Protection and Affordable Care Act of 2011 is one example of how the government has responded to support this initiative. New reimbursement models issue payment based on pre-determined quality metrics, which have spiked growth in patient-centered medical homes (PCMH).[8] PCMHs emphasize holistic, quality care that is accessible, coordinated, efficient, preventative, and team-based, involving physicians, nurses, pharmacists, behavioral health specialists, and social

workers.[9-11] This movement requires healthcare delivery that is efficient and accountable, reducing gaps in care.

In light of these changes and effects on the healthcare system, a declining primary care physician supply is particularly challenging. It is estimated that by 2032, the primary care physician shortfall range will be between 21,100 and 55,200.[12] This expected shortage is driven by many factors including the aging and growing U.S. population, physician retirement, and the increasing complexity of patients' health care needs. In fact, about 40% of the entire physician workforce is expected to retire in the next decade. This will place significant strain on primary care in years to come as we continue to battle complex, progressive chronic diseases such as diabetes in an aging population. This only further highlights the importance of primary care teams utilizing mid-level healthcare providers, such as pharmacists. Notably, the U.S. Surgeon General considers pharmacists to be underutilized and supports their incorporation into primary care teams to help improve safety and quality as well as alleviate provider shortage and costs.[13]

PHARMACIST UTILIZATION IN PRIMARY CARE

With time, many advancements in pharmacy practice have occurred and roles of the pharmacist have expanded drastically beyond traditional medication dispensing. One example is ambulatory care clinical pharmacy, which is a rapidly growing area of specialization today. Ambulatory care clinical pharmacy specialists provide direct patient care and are trained in chronic disease management, including but not limited to type 2 diabetes (T2DM), hypertension, and hyperlipidemia. In 2018, there were >3,800 Board Certified Ambulatory Care Pharmacists (BCACPs), which represents a >17% increase from 2017.[14] This growth will likely lead to many future opportunities for pharmacists to aid in primary care and will thereby increase access to

care for patients. In the Veteran's Affairs (VA) Health System, for example, clinical pharmacists reduce primary care provider revisit rates, improve same-day availability, and reduce wait time for new patients.[15] Clinical roles of ambulatory care pharmacists include medication optimization, medication and disease management involving patient assessment and lab monitoring, patient education, and quality metric improvement, all of which contribute to continuity of care and overall health care efficiency.[16]

The role of ambulatory care pharmacists varies by practice site. Pharmacist participation in PCMHs, assisting with disease state management and medication therapy management, has proven to be beneficial for a variety of disease outcomes including diabetes, hypertension, and heart failure.[17-25] Much of this is accomplished through collaborative drug therapy management (CDTM), which allows for pharmacists to assume a larger role in patient care especially for chronic diseases like T2DM.[26-28] In different scenarios, pharmacists may be granted independent prescribing privileges, such as in the VA Health System, or they may participate in shared appointments with the provider where they can make therapeutic recommendations as necessary.[21,26-28] Others allow for pharmacists to meet with patients independently without prescribing privileges; all recommendations must be presented to the provider for approval.[21] Finally, there can be a Collaborative Practice Agreement (CPA), which is a formal relationship between the pharmacist and physician that outlines the pharmacist's roles and responsibilities in patient care. Specific responsibilities differ depending on the protocol as defined by the primary care physician but often include initiation of new therapy, adjustment of current therapy, and ordering of pertinent labs.[29] This allows pharmacists to follow-up with patients independently and implement care decisions to improve outcomes. This is especially useful in diabetes

management as it leads to increased appointments and, therefore, improved access to medical care. In three studies, for example, diabetic patients averaged ≥6 office visits with the ambulatory pharmacist per year, which allows for timely dose adjustments, appropriate monitoring, and patient encouragement.[30-32] Through these various new practice models, pharmacists can effectively manage T2DM in the outpatient setting; however, patient referral to the pharmacist often depends on provider discretion, which may prevent some patients from reaping this benefit. It is clear that in today's healthcare landscape and through various clinical structures, pharmacists are an important resource on the medical team who can help manage a variety of chronic diseases, including T2DM.

Chapter Two: An Integrated Approach to Diabetes Management

DIABETES AND ASSOCIATED CONCERNS

Diabetes mellitus, with T2DM accounting for the majority of cases, is a prevalent and costly chronic disease in the U.S. Diabetes affects over 30 million people with total annual costs estimated at $327 billion in 2017.[33,34] Further, estimated costs from both diagnosed and undiagnosed diabetes exceed $400 billion, and medical costs for those with diabetes are more than twice that for patients without diabetes.[34-36]

T2DM is a complex chronic disease that has deleterious effects on multiple bodily organs, and is a major cardiovascular mortality risk factor.[37-39] Recent data show that even when adjusting for other cardiovascular disease risk factors, diabetes alone increases the risk of death by 18%.[40] Further, the risk of mortality increases proportionally to worsened glucose control as demonstrated by higher mortality rates observed at progressive increases in A1C ≥7%. In fact, each 1% reduction in the A1C value can reduce the risk of microvascular complications by 37% and the risk of mortality by 21% without any observed limit of glycemia to provide benefit.[41] This proves that the A1C value is an important marker of clinical response when managing T2DM and that percentage decreases are significant regardless of baseline A1C values. As a cause of death, diabetes itself is often underreported and likely represents a contributing cause of death in most cases, yet it still remains the seventh leading cause of death in the U.S.[42,43] With the projected primary care physician shortfall and heightened healthcare burden, T2DM will continue to place a large strain on the healthcare system in the U.S. Therefore, comprehensive diabetes management, utilizing team members such as pharmacists, is essential in order to address system-wide challenges imposed by this disease and to improve patient health and mitigate complications.

PHARMACIST-MANAGED DIABETES CARE

Diabetes management is complex and time-consuming, requiring persistence from both the patient and healthcare provider. Increased complexity is illustrated by more than seven drug classes available to treat T2DM and the numerous complications of uncontrolled T2DM affecting several bodily systems, including but not limited to neurological, renal, and cardiovascular systems.[34,44-46] Difficulty reaching therapeutic goals can be attributed to factors such as complex therapies, poor medication adherence, concerning side effects, and financial burdens.[47,48] With medication therapy as the hallmark in diabetes treatment after lifestyle modification, ambulatory care clinical pharmacists are well-trained to assist in appropriate therapy selection and to address drug-related concerns.

The Asheville Project in 1996 first demonstrated the positive effects pharmacists can have on diabetes outcomes when integrated into healthcare teams.[49] The pharmacists involved in this study provided cognitive services for patients including glucometer training, general diabetes education, and clinical assessment. Improvements in A1C, total cholesterol, and low-density lipoprotein (LDL) were shown over 14 months as well as decreased costs by $472 per patient per year. For example, at each follow-up the percentage of patients who improved or lowered the A1C was more than 50%, demonstrating persistent positive effects of pharmacists over time. In addition, pharmacists improve standards of diabetes care, as recommended by the American Diabetes Association, compared to usual care including timely A1C measurement (91.2% vs. 76.7%; P=0.0013), lipid measurement (95.6% vs. 70.0%; P<0.0001), microalbumin screening (75.2% vs. 15.7%; P<0.0001), foot exams (87.6% vs. 47.6%; P<0.0001), and pneumococcal (80.5% vs. 37.6%; P<0.0001) and influenza vaccines (74.3 vs. 50.0%; P<0.0001).[50] Meeting these standards are critical in maintaining the overall health of the diabetic patient. A recent

meta-analysis, including ≥7000 patients ≥18 years old with type 1 or 2 diabetes, assessed the impact of pharmacists on diabetes outcomes in ambulatory settings. Compared to usual care, pharmacists lowered the A1C from baseline by 1.1% (95% CI, 0.88-1.27) with an overall standardized mean difference of 0.56 (P<0.001), indicating a significant and moderate effect.[21] Significant reductions were demonstrated across age groups and baseline A1C values. Pharmacists also improved cardiovascular disease risk factors in these patients. In the same study, pharmacist interventions reduced LDL cholesterol [-10.6 mg/dL (95% CI, -7.1 to -14.1)] and systolic blood pressure values (SBP) [SBP -4.3 mm Hg (95% CI, -4.3 to -6.2)] with differences compared to usual care. A second systematic review and meta-analysis including 15 randomized controlled trials with >9,000 patients showed that pharmacists practicing independently or in conjunction with other medical professionals led to significant reductions in risk factors compared to usual care, including SBP (-6.2 mm Hg [95% CI, -7.8 to -4.6]), diastolic blood pressure (DBP) (-4.5 mm Hg [95% CI, -6.2 to -2.8]), and LDL cholesterol (-11.7 mg/dL [95% CI, -15.8 to -7.6 mg/dL]).[51] Further, pharmacists have also shown to be cost-effective for disease management including diabetes and hypertension, with benefit-to-cost ratios ranging from 1:1 to 8.5:1 for diabetes.[52,53] In the VA Health System, for example, pharmacist visits cost about $15,000 less compared to primary care physician visits per 1,000 30-minute encounters.[15] These data provide evidence that pharmacists can improve diabetes outcomes and help achieve standards of care while mitigating costs, and support their inclusion and importance on the medical team.

Currently, most clinical pharmacists see patients based on a physician referral system; however, it is unclear which patients are most likely to benefit from these services. In 2017, Lam

and colleagues evaluated predictors of response to pharmacist involvement in diabetes management.[54] This was a retrospective cohort study including three treatment facilities in a united health system in Cleveland, Ohio. The pharmacists providing care operated under a CPA allowing for independent patient visits and prescribing privileges within the scope of practice. Included patients were >18 years old and had an A1C ≥9% at baseline. Response to the clinical pharmacist was defined as a decrease in the A1C by ≥2% or achieving an A1C <8% one year after the first visit. Failing to respond to these A1C goals or loss to follow-up qualified as a non-responder in the study. The authors found a history of cerebrovascular accident (CVA) (AOR 2.7; 95% CI, 1.2-5.9), bolus insulin at baseline (AOR 0.5; 95% CI, 0.4-0.8), and baseline A1C (AOR 1.2; 95% CI, 1.1-1.3) to be independently predictive of response. CVA and baseline A1C were positive predictors of response, whereas bolus insulin at baseline was associated with therapeutic failure. This study had a meaningful and clinically significant definition of success. While this was the first study to specifically assess predictors of response to pharmacist-managed diabetes care, it did not assess interventions made during the study period and only assessed baseline patient demographics and clinical data. Additionally, sodium-glucose cotransporter-2 (SGLT-2) inhibitors were absent from this study due to timing of Food and Drug Administration (FDA) approval. Lastly, the study endpoint was one year after the initial pharmacist visit and included patients even if they only had a single visit, providing potentially weak association to the pharmacist interventions one year prior to the study outcome. While helpful to address this research question, additional studies are needed to provide more conclusive evidence in order to better identify patients and interventions associated with therapeutic response.

Chapter Three: Objectives and Hypotheses

KNOWLEDGE GAP

There is a lack of standardization or guidance in referring patients to the clinical pharmacist for T2DM management, which likely results in patients missing out on this beneficial service. Predictive analytics are useful to help inform health organizations which patients should be targeted for higher levels of care in order to improve healthcare efficiency. Specifically, it would be useful to know which patients and which specific clinical interventions are most likely to demonstrate benefit from pharmacy services. In doing so, this can help increase the number of physician referrals, expand access to care, and ultimately, improve patient outcomes.

To our knowledge, only one study has assessed patient predictors of response to diabetes care provided by a clinical pharmacist.[54] Our study will build on this research by assessing both baseline patient characteristics and clinical interventions made in a diverse population. This will allow for a more thorough approach to determining variables implicated in clinical response. It will also be a reflection of medications currently used in practice to treat T2DM, including SGLT-2 inhibitors. The study findings can help influence protocols for physician referral to the clinical pharmacist for T2DM management, reaching patients most likely to benefit who may otherwise have no exposure to this service. Further, this study will help identify specific clinical interventions that are associated with response in our patient population. Thus, the goals of this study are to identify predictors of response to pharmacist-led diabetes care in order to better identify high-risk patients who would benefit from referral to the clinical pharmacist and to elucidate specific interventions that provide most benefit.

OBJECTIVE 1

Describe clinical responses to pharmacist-led diabetes care.

HYPOTHESIS 1

Responders, based on study definitions, will represent about 45% of the patient population in this study.

OBJECTIVE 2

Identify patient characteristic and interventional variables that are predictive of clinical response to pharmacist-led diabetes care.

HYPOTHESIS 2

Higher baseline A1C, a lack of bolus insulin at baseline, and assistance with financial barriers will be positive predictors of therapeutic response.

Chapter Four: Methods

Study Setting and Design

This study analyzed patients referred to an ambulatory care clinical pharmacist for evaluation and management of T2DM in San Antonio, Texas. The two pharmacists providing care during the study period had Doctor of Pharmacy degrees as well as residency training and board certification in ambulatory care. Study sites included The University of Texas Health Medical Arts and Research Center Primary Care Center, The University of Texas Health Medical Drive Primary Care Center, and the University Health System Robert B. Green Family Medicine Clinic. All three study sites had established CPAs in place between the pharmacist and primary care physicians, which allowed the pharmacist to meet independently with patients, evaluate treatment, and make therapeutic adjustments and schedule follow-up appointments as necessary.

This study was a retrospective cohort study. Patients were eligible if they were ≥18 years old at time of referral and had a referral to the pharmacist for T2DM management. Included patients had at least one completed visit with the pharmacist between January 1, 2015 and December 31, 2018. We excluded patients diagnosed with gestational diabetes or type 1 diabetes, a visit with an endocrinologist during the study period, a baseline A1C <7%, or an absent A1C value at baseline or at follow-up. We also excluded patients who previously sought care from the pharmacist before the study period and were subsequently referred again to the pharmacist. If patients had a consult order placed but no completed initial visit with the pharmacist, they were excluded. Clinical response was defined as a reduction in the A1C value by ≥1% from baseline or meeting the documented A1C goal between 3 and 6 months from the baseline A1C value. Non-responders were defined as failing to meet these A1C goals.

DATA COLLECTION AND ANALYSIS

We gathered data from the Sunrise electronic health record for University Health System and EPIC for University of Texas Health clinics. Patients were identified by having a physician consult order in place to the clinical pharmacist. Data were extracted at baseline, during the study period (per subject – the 6 months following the first visit with the pharmacist), and at the end of the study (Figure 1). Baseline variables were collected up to one year prior to the first visit with the pharmacist. Medical record numbers were stored in a protected study key and were reassigned to a new study code number. Only the primary investigator had access to the study key and only one copy of the key existed. We stored our collected data in Research Electronic Data Capture (REDCap).[55] Variables included demographics (age, sex, ethnicity), weight, body mass index (BMI), preferred language, smoking status, employment, comorbidities, vital signs, laboratory values, duration of diabetes, clinic location, number of visits completed with pharmacist, number of visits completed with primary care physician or provider, pharmacist interventions, and medical therapy (Table 1). We also collected insurance type including public, private, or none (i.e., self-pay). Specific to Bexar County, Texas, CareLink enrollment was captured as well. CareLink is not an insurance program but instead is a patient assistance program funded by the county that provides significant financial assistance for medical care to patients in need; patients can often receive prescription medications for copays as low as $0 depending on certain criteria. CareLink is not available for people with public or private insurance or people living outside of Bexar County.

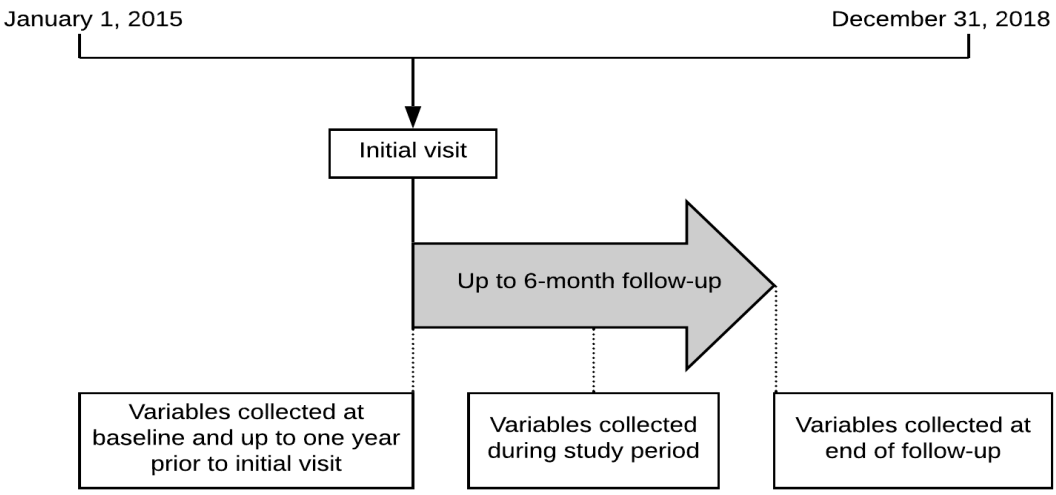

Figure 1. Study Timeline

Table 1. Definitions and Timeframes for Collected Variables

Variable Name	Definition*
Baseline A1C	A1C value prior to and closest to first completed pharmacist visit
Number of medications at baseline	Scheduled medications listed on patient's outpatient medication list including scheduled prescription and over-the-counter medications (does not include as needed medications or duplicate therapies)
Diabetes medications at baseline	Medications listed on patient's outpatient medication list used to treat T2DM
Comorbidities at baseline	Comorbidities in the Charlson Comorbidity Index[56] which include: -Hypertension -Hyperlipidemia -History of myocardial infarction -History of cerebrovascular accident -Congestive heart failure -Liver disease -Retinopathy -Nephropathy or chronic kidney disease -Neuropathy -Dementia -Chronic obstructive pulmonary disease -Cancer or any malignancy -HIV/AIDS
Blood pressure	Blood pressure measured in mm Hg

Table 1. Definitions and Timeframes for Collected Variables, Cont.

Microalbuminuria	Presence or absence of microalbuminuria (30-299 mg/g creatinine in urine)
Serum creatinine	Serum creatinine laboratory value (mg/dL)
eGFR	eGFR laboratory value (mL/min/1.73m^2)
AST	AST laboratory value (Units/L)
ALT	ALT laboratory value (Units/L)
LDL cholesterol	LDL laboratory value (mg/dL)
HDL cholesterol	HDL laboratory value (mg/dL)
Total cholesterol	Total cholesterol laboratory value (mg/dL)
TG	TG laboratory value (mg/dL)

Abbreviations: T2DM, Type 2 Diabetes Mellitus; HIV, Human Immunodeficiency Virus; AIDS, Acquired Immune Deficiency Syndrome; eGFR, estimated glomerular filtration rate; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDL, low-density lipoprotein; HDL, high-density lipoprotein; TG, triglycerides

*Data were collected either at baseline (first visit with pharmacist) or at the time point closest to baseline and up to one year prior to the first visit

Pharmacist interventions for diabetes care were gathered from recorded information in patient encounter notes. These included actions such as starting or discontinuing a medicine, adjusting a dose, and providing self-monitored blood glucose counseling. It also included referral to resources including a dietician or a community-based twelve-step program called Overeaters Anonymous. Of note, medication optimization in this study refers to a reduction in the number of times per day a patient takes medications. For example, if a patient takes medications three times per day and this can be further simplified to once or twice per day, this intervention would be recorded as medication optimization.

Descriptive analyses were conducted on all collected variables. Nominal data were analyzed between responders and non-responders using either the chi-square or Fisher's exact test as appropriate. Ordinal and continuous data were analyzed using either the Wilcoxon rank sum or Student t-test as appropriate. A p-value of <0.05 was considered significant on bivariable analysis. Multivariable logistic regression analyses were conducted on collected covariates

demonstrating a p-value <0.20 on bivariable analysis in order to determine significant predictors of response. Variables meeting a threshold of $p<0.05$ in the logistic regression model were considered independent predictors of response. We utilized JMP software (JMP Pro Version 14.0.0) for data analysis. Sample size was determined based on a two sample proportions calculation. Based on previous literature, we estimated that 45% of patients will be considered "responders" to pharmacy interventions.[54] We also predicted that a clinically significant difference for any one covariate to be a 20% difference between a responder and non-responder. Given this information with an alpha of 0.05 and power of 80%, 178 patients were required to detect a 20% difference between responders and non-responders for any given covariate.

Chapter Five: Results

The total number of referrals made to the pharmacists during the study period was 1,216 among the three clinic sites. The primary investigator screened 700 patient records and ultimately excluded 520 (Figure 2). Table 2 describes the common reasons for study exclusion among patients with a T2DM referral. Of these referrals, 180 patients met inclusion criteria and were included in this study. Patients were predominantly English-speaking, obese, Hispanic females (Table 3). Most patients had metformin treatment at baseline and the end of the study. Concomitant chronic diseases, including hypertension and hyperlipidemia, were prevalent.

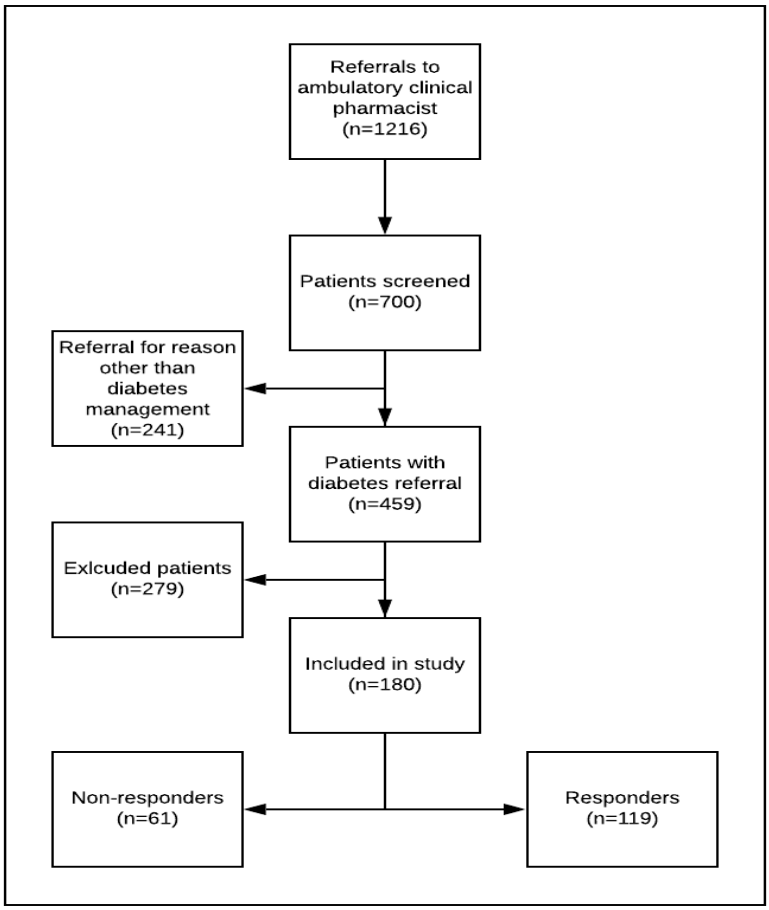

Figure 2. Patient flowchart.

Table 2. Reasons for Study Exclusion

Reason for Study Exclusion	Number of Excluded Patients (n=279)
Absent baseline A1C	22
Baseline A1C <7%	17
Absent follow-up A1C	38
First visit outside study timeframe	82
Consultation with endocrinology	10
First visit not completed	110

Table 3. Characteristics of Study Cohort

Characteristic	Overall (n = 180)	Responders (n = 119)	Non-Responders (n = 61)	P-value
Age (years)	56 ± 11	55 ± 11	57 ± 10	**0.119**
Weight (kg)	90 (74-103)	90 (74-105)	92 (74.5-100)	0.749
BMI (kg/m^2)	33 (28.7-38.2)	32.4 (28.3-38.3)	33.3 (29.5-38.3)	0.637
Obesity (BMI ≥30)	126 (70)	81 (68.07)	45 (73.77)	0.426
Male	67 (37.2)	44 (36.97)	23 (37.70)	0.924
Ethnicity Hispanic	103 (58)	64 (53)	39 (65)	**0.167**
Preferred Language English Spanish Other	 140 (78) 36 (20) 4 (2)	 93 (78) 23 (19) 3 (3)	 47 (77) 13 (21) 1 (2)	0.890
Clinic Location UT UHS	 91 (51) 89 (49)	 55 (46) 64 (54)	 36 (59) 25 (41)	**0.103**
Employment Yes No	 64 (36) 116 (64)	 40 (40) 60 (60)	 16 (35) 30 (65)	0.546
Insurance Type Public Private Self-pay	 85 (49) 53 (30) 37 (21)	 56 (48) 37 (32) 23 (20)	 29 (49) 16 (27) 14 (24)	0.881
CareLink	37 (21)	23 (19)	14 (23)	0.572
Past or Current Smoker	64 (36)	40 (34)	24 (39)	0.449
Baseline SBP	129.5 (119-143)	128 (119-140)	133 (120.5-147)	**0.083**
Baseline DBP	72.3 ± 10.3	72.82 ± 9.71	71.36 ± 11.29	0.805
Duration of Diabetes ≥10 years	107 (67)	64 (62)	43 (74)	**0.118**

Table 3. Characteristics of Study Cohort, Cont.

Baseline A1C	9.9 (8.5-11.2)	10.1 (8.9-12.2)	9.0 (8.45-10.5)	**0.003**
Microalbuminuria	81 (50)	53 (50)	28 (51)	0.913
eGFR >60 mL/min/1.73m^2	137 (78)	92 (79)	45 (75)	0.517
SCr	0.85 (0.7-1.08)	0.87 (0.71-1.07)	0.81 (0.67-1.09)	0.602
AST	20 (15-31)	20 (16-34)	20 (15-25)	**0.137**
ALT	28 (20-41)	29 (20-44)	26 (20-35)	**0.168**
LDL	92 (62-125)	92 (61.5-118.5)	91 (66-131)	0.876
HDL	43 (36-53)	42 (36-52)	44 (36-54)	0.283
Total Cholesterol	172 (134-205)	171 (131-205)	172 (135-224)	0.712
Triglycerides	159 (108-262)	164 (114-263)	147 (92-254)	**0.139**
Comorbidities				
Hypertension	146 (81)	92 (77)	54 (89)	**0.060**
Hyperlipidemia	159 (88)	107 (90)	52 (85)	0.363
MI	9 (5)	6 (5)	3 (5)	0.971
CVA	15 (8)	10 (8)	5 (8)	0.962
CHF	12 (7)	6 (5)	6 (10)	0.234
Liver Disease	18 (10)	11 (9)	7 (11)	0.640
Retinopathy	29 (16)	14 (12)	15 (25)	**0.030**
Nephropathy or CKD	44 (24)	29 (24)	15 (25)	0.974
Neuropathy	64 (36)	39 (33)	25 (41)	0.278
Dementia	0	0	0	
COPD	10 (6)	5 (4)	5 (8)	0.281
Cancer or Malignancy	13 (7)	7 (6)	6 (10)	0.342
HIV/AIDS	0	0	0	
None	4 (2)	2 (2)	2 (3)	0.503
Number of Comorbidities	3 (2-4)	3 (2-4)	3 (2-4)	**0.083**
Hospital or ER admission at baseline	50 (28)	30 (25)	20 (33)	0.286
Hospital or ER admission during follow-up	26 (14)	14 (12)	12 (20)	**0.161**
Anti-Diabetic Medications at Baseline				
Metformin	129 (72)	91 (76)	38 (62)	**0.048**
TZD	25 (14)	15 (13)	10 (16)	0.491
SGLT-2 Inhibitor	12 (7)	7 (6)	5 (8)	0.544
GLP-1 Receptor Agonist	14 (8)	7 (6)	7 (11)	0.240
DPP-4 Inhibitor	38 (21)	25 (21)	13 (21)	0.962
Sulfonylurea	33 (18)	18 (15)	15 (25)	**0.127**
Meglitinide	2 (1)	1 (1)	1 (2)	1.000
Basal insulin	98 (54)	68 (57)	30 (49)	0.310
Bolus insulin	49 (27)	24 (20)	25 (41)	**0.004**
None	3 (2)	3 (3)	0	0.552

Table 3. Characteristics of Study Cohort, Cont.

Insulin at Baseline	104 (58)	68 (57)	36 (59)	0.809
Injectable at Baseline	110 (61)	70 (59)	40 (66)	0.377
Number of Anti-Diabetic Medications at Baseline	2 (2-3)	2 (2-3)	2 (2-3)	0.234
Notable Baseline Medications				
Antipsychotic	13 (7)	11 (9)	2 (3)	0.224
Oral corticosteroids	4 (2)	3 (3)	1 (2)	1.000
Lithium	1 (1)	1 (1)	0	1.000
Hormone Replacement	4 (2)	1 (1)	3 (5)	**0.114**
Calcineurin inhibitor	2 (1)	1 (1)	1 (2)	1.000
Number of Baseline Medications	7 (5-10)	7 (5-10)	7 (6-10)	0.681
Anti-Diabetic Medications at End of Study				
Metformin	140 (78)	99 (83)	41 (67)	**0.017**
TZD	39 (22)	24 (20)	15 (25)	0.499
SGLT-2 Inhibitor	37 (21)	26 (22)	11 (18)	0.546
GLP-1 Receptor Agonist	55 (31)	37 (31)	18 (30)	0.827
DPP-4 Inhibitor	40 (22)	27 (23)	13 (21)	0.833
Sulfonylurea	15 (8)	8 (7)	7 (11)	0.285
Meglitinide	2 (1)	1 (1)	1 (2)	1.000
Basal insulin	120 (67)	76 (64)	44 (72)	0.262
Bolus insulin	41 (23)	23 (19)	18 (30)	**0.128**
None	0	0	0	
Insulin at End of Study	121 (67)	77 (65)	44 (72)	0.312
Injectable at End of Study	136 (76)	88 (74)	48 (79)	0.480
Number of Anti-Diabetic Medications at End of Study	3 (2-4)	3 (2-4)	3 (2-4)	0.728

Abbreviations: BMI, body mass index; UT, University of Texas; UHS, University Health System; SBP, systolic blood pressure; DBP, diastolic blood pressure; A1C, hemoglobin A1c; eGFR, estimated glomerular filtration rate; SCr, serum creatinine; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDL, low-density lipoprotein; HDL, high-density lipoprotein; MI, myocardial infarction; CVA, cerebrovascular accident; CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency disease; AIDS, acquired immunodeficiency syndrome; IQR, interquartile range; ER, emergency room; TZD, thiazolidinedione; SGLT-2, sodium-glucose co-transport-2; GLP-1, glucagon-like peptide 1; DPP-4, dipeptidyl peptidase-4

All data are represented as n (%) unless stated otherwise.

Age and diastolic blood pressure are represented as mean ± standard deviation. All other listed continuous variables are represented as median (IQR).

Altogether, 119 patients (66%) were considered responders to clinical pharmacist interventions for diabetes care. Of the responders, 110 patients (92%) had a decrease in the A1C value by ≥1% and 9 patients (8%) met their documented goal without this threshold change in A1C. Fifty-one patients reached their documented A1C goal during the study. The median (IQR) change in A1C from baseline for responders and non-responders was -2.2% (-3.7 to -1.3) and 0.4% (-0.4 to 1.05) (P<0.001), respectively. The most common types of interventions were starting a new medication, making a dose adjustment, discontinuing a medication, and providing a blood glucose log in 73%, 57%, 48%, and 37% of patients, respectively. Responders and non-responders did not differ significantly based on age, gender, ethnicity, preferred language, weight, insurance type, smoking status, or comorbidity type except for retinopathy. Non-responders were more likely to have retinopathy at baseline compared to responders (24.6% vs. 11.8%, P=0.030). Lab values were similar between groups except for baseline A1C, which was significantly elevated for responders (10.1% vs. 9.0%, P=0.0026) (Table 3). Overall utilization rates of insulin and sulfonylureas decreased in the study cohort from baseline to end of study (Figure 3). Metformin use was more common among responders at both baseline (76.5% vs. 62.3%, P=0.048) and end of study (83.2% vs. 67.2%, P=0.017) compared to non-responders. Further, bolus insulin use at baseline was more common among non-responders (41% vs. 20.2%, P=0.004). The only recorded pharmacist intervention that was significantly different between groups was medication optimization among responders compared to non-responders (11.8% vs. 1.6%, P=0.009) (Table 4). Lastly, responders demonstrated a significantly different median number of completed visits with the pharmacist (2 (1-3) vs. 2 (1-2), P=0.0217), and the mean number of visits between these groups were 2.4 and 1.96 (P<0.006), respectively.

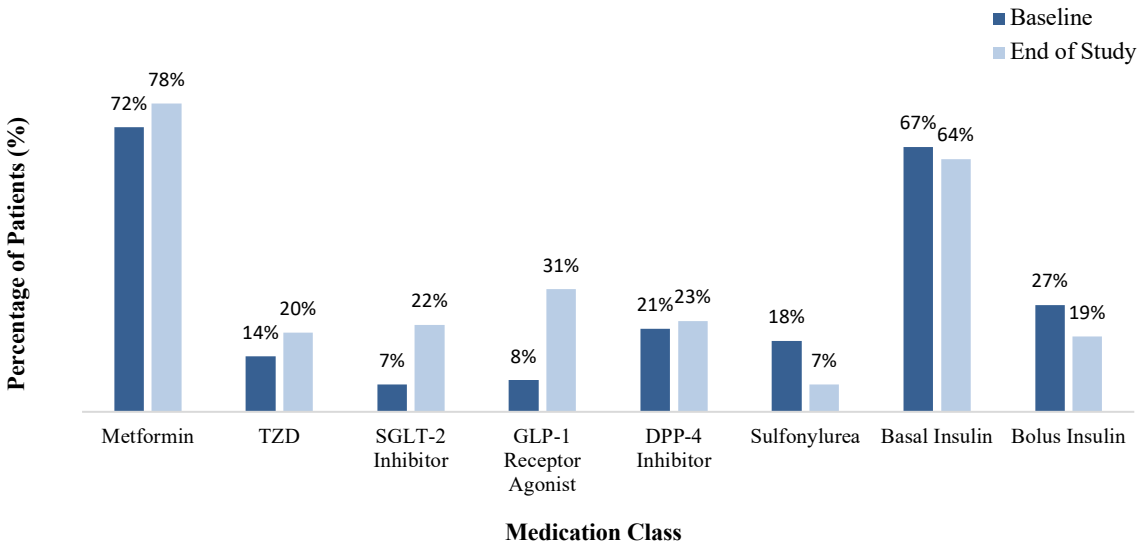

Figure 3. Medication Changes in Overall Cohort at Baseline and End of Study

Table 4. Baseline and Interventional Diabetes Care.

Measure	Overall (n = 180)	Responders (n = 119)	Non-Responders (n = 61)	P-value
Number of Completed Visits with Pharmacist	2 (1-3)	2 (1-3)	2 (1-2)	**0.022**
Number of Completed Visits with PCP	2 (1-3)	1 (0-2)	2 (1-3)	**0.121**
Pharmacist Interventions				
Started New Medication	132 (73)	87 (73)	45 (74)	0.924
Dose Adjustment	102 (57)	72 (61)	30 (49)	**0.148**
Discontinued Medication	87 (48)	56 (47)	31 (51)	0.633
Provided BG log and SMBG	67 (37)	49 (41)	18 (30)	**0.122**
Counseling				
Referral to Dietician	15 (8)	13 (11)	2 (3)	**0.059**
Referral to OA	16 (9)	12 (10)	4 (7)	0.421
Assistance with Financial Barriers	23 (13)	15 (13)	8 (13)	0.923
Provided Pillbox	10 (6)	7 (6)	3 (5)	1.000
Medication Optimization	15 (8)	14 (12)	1 (2)	**0.009**
Provided Medication Action Plan or Calendar	14 (8)	11 (9)	3 (5)	0.388

Abbreviations: PCP, primary care provider; BG, blood glucose; SMBG; self-monitored blood glucose; OA, overeaters anonymous
All listed nominal variables are represented as n (%) unless stated otherwise.
All listed continuous variables are represented as median values (IQR).

Twenty-five variables were included in the multivariable logistic regression analysis in order to determine predictors of response to the clinical pharmacist as shown in Table 5. Significant predictors included baseline A1C (OR 1.41; 95% CI 1.08-1.85), number of completed visits with both the primary care provider (OR 0.69; 95% CI 0.49-0.96) and the pharmacist (OR 1.65; 95% CI 1.03-2.64), and medication optimization (OR 10.68; 95% CI 1.04-109.9). All mentioned significant variables, except for number of completed visits with the PCP, were positive predictors of response. All other variables inputted into the logistic regression model were not associated with response in the primary outcome.

Table 5. Multivariable Logistic Regression Model for Predictors of Response

Characteristic	Odds Ratio	95% CI	P-value
Sulfonylurea at baseline	0.33	0.10-1.02	0.055
Bolus insulin at baseline	0.24	0.06-1.02	0.053
Baseline A1C (per percentage point >7%)	1.41	1.08-1.85	**0.013**
Completed visits with pharmacist (per additional visit)	1.65	1.03-2.64	**0.037**
Completed visits with PCP (per additional visit)	0.69	0.49-0.96	**0.029**
Medication optimization	10.68	1.04-109.9	**0.046**
Age (per additional year)	1.02	0.97-1.08	0.337
Number of comorbidities (per additional comorbidity)	1.00	0.63-1.60	0.987
Baseline SBP (per additional mm Hg)	1.00	0.97-1.03	0.962
AST (per additional unit)	1.03	0.97-1.10	0.290
ALT (per additional unit)	0.99	0.96-1.03	0.641
Triglycerides (per additional unit)	1.00	1.00-1.00	0.818
Clinic location (UT vs. UHS)	0.72	0.25-2.05	0.538
DM duration (<10 vs. ≥10 years)	1.52	0.52-4.46	0.446
Hypertension	0.66	0.14-3.11	0.594
Retinopathy	0.73	0.17-3.20	0.675
Hospital admission during follow-up	0.61	0.18-2.07	0.431
Metformin at baseline	0.89	0.22-3.54	0.864
Hormonal replacement at baseline	0.27	0.02-4.26	0.351
Metformin at end of study	2.08	0.49-8.86	0.320
Bolus insulin at end of study	1.52	0.35-6.60	0.578
Dose change	1.18	0.43-3.22	0.749
BG log and SMBG counseling	1.36	0.50-3.72	0.549
Referral to dietician	1.99	0.30-13.31	0.477
Ethnicity (non-Hispanic vs. Hispanic)	1.62	0.60-4.36	0.339

Chapter Six: Discussion

This retrospective cohort study involving patients seeking care for T2DM by a clinical pharmacist in two different health systems in San Antonio, Texas demonstrates not only the effectiveness of this clinical service, but also specific characteristics and interventions that predict therapeutic response. Nearly two of every three patients were considered responders in this study, demonstrating a higher response rate than shown previously.[54] Further, the median change in A1C from baseline amongst responders was -2.2%, which is considerable and clinically significant especially given a short six month maximum follow-up. These results demonstrate the effectiveness of our ambulatory clinical pharmacy services for T2DM management. We discovered that higher baseline A1C, more visits with the pharmacist, fewer visits with the PCP, and medication optimization were all independently predictive of clinical response.

Clinical pharmacists have been involved in chronic disease management, specifically T2DM, for many years, but is not clear exactly which patients benefit most or which interventions are most effective. Similar to the study by Lam, et al., a higher baseline A1C was predictive of response in our study; however, their study did not assess clinical interventions made. Higher baseline A1C values have consistently been shown to predict a larger decrease in A1C compared to lower baseline A1C and elicit increased effectiveness of anti-diabetic medications.[57-61] Interestingly, bolus insulin at baseline was not statistically significant as in the previous study but trended towards significance as a predictor of non-response in our study. Perhaps a larger sample size would result in statistical significance. With many other therapeutic options recommended by guidelines prior to bolus insulin, its use may be representative of exhausted medication trials, progression of clinical disease, or a last resort.[45] Requirement of bolus insulin may also indicate higher levels of insulin resistance and progression of disease. Lastly, bolus insulin often requires multiple injections per day, which is likely to limit adherence to therapy and ultimately reduce therapeutic benefit. Similarly, sulfonylurea use at baseline was not a statistically significant

predictor of response but trended towards significance. Their use was notably reduced for all patients at the end of study compared to baseline. The unfavorable use of sulfonylureas can be attributed to their reduced effectiveness over time and negative adverse effects.[62] These agents act directly on pancreatic beta cells, placing them under additional strain and ultimately catalyzing their dysfunction. Unlike the study by Lam, et al., we did not find a history of CVA to be a predictor of response. In fact, no specific comorbidities were associated with response or non-response in the logistic regression model even though retinopathy was significantly increased amongst non-responders on bivariate analysis.

Analyzing the medication classes between responders and non-responders from baseline compared to end of study provides useful information as well. First, metformin use was significantly elevated amongst responders at both baseline and end of study; however, it was not independently predictive of response. Nevertheless, this highlights the first-line use of metformin for all patients as appropriate given its affordability, high efficacy, and established safety. Medication classes considered second-line including SGLT-2 inhibitors, GLP-1 receptor agonists, and TZDs are all numerically increased at end of study compared to baseline for the overall cohort. This demonstrates the pharmacist's efforts to add appropriate guideline-recommended medications in order to achieve clinical response.

Increased number of visits with the pharmacist was predictive of clinical response. While the median number of visits did not numerically differ between groups, the mean was slightly elevated in the responder group. This indicates that while specific interventions may not demonstrate benefit in our study, the education received and interactions with a pharmacist are therapeutically beneficial. The one recordable pharmacist intervention associated with clinical response was medication optimization. Complex medication regimens with multiple dosing times per day can contribute to medication nonadherence. Pharmacists in the study utilized medication optimization in order to ensure treatment adherence and convenience. This demonstrates the

importance and critical role of pharmacists with detailed knowledge and attention regarding medication dosing and interactions. This intervention should be emphasized at all patient visits. Interestingly, more visits with the PCP was a negative predictor of response in this study. While the explanation for this finding is unclear, it may reflect acute concerns needing to be addressed during the study, which could hinder the time and attention spent on T2DM management. In addition to showing positive effects on A1C levels, pharmacists can also reduce gaps in care and help achieve quality standards.[25] Many of these interventions and effects were not measured or reported in this study.

There are several strengths to this study. First, the results provide real world data involving all anti-diabetic medication classes currently available. Further, this study involves patients with a broad range of socioeconomic statuses from two health systems increasing its generalizability. The relatively short follow-up time more strongly reflects the effect of pharmacist interventions compared to studies with longer follow-up, especially if patients only complete one visit. This ultimately strengthens the conclusions of the study. Lastly, this study considered both baseline and interventional data in order to predict therapeutic response, providing a comprehensive interpretation of patient care and study results.

This study also has potential limitations. First, it is limited due to its retrospective nature, which is prone to missing data, inaccurate data reporting, and misclassification bias. For example, an intervention may have occurred but was not explicitly recorded in the patient's clinical note and would, therefore, not be considered. In addition, due to the nature of the study, certain clinical interventions made may not be recordable and consequently cannot be included in the analyses. For example, while referral to a dietician can be recorded, specific dietary recommendations made by the pharmacist were not recorded. It is expected that dietary recommendations, which are essential in diabetes treatment, are made at each visit; however, the extent of these recommendations are not easily quantified into recordable research data. Further, since patients

are referred to the clinical pharmacist based on provider discretion, this could lead to selection bias; each referring physician may create a consultation referral based on different factors, which may influence the results to an unknown extent. Our findings may have limited generalizability to the U.S. population given its high rate of Hispanic ethnicity of 58%. Importantly, ethnic differences may influence results based on varying beliefs regarding treatment and health care in general.

Chapter Seven: Conclusion and Future Directions

This study demonstrates the effectiveness of ambulatory clinical pharmacists in T2DM management and sheds light on specific patient characteristics and clinical interventions that help predict therapeutic response. Nearly two-thirds of patients were considered responders in this study, which is greater than shown in previous studies. We found that higher baseline A1C, more visits with the pharmacist, fewer visits with the PCP, and medication optimization were all associated with clinical response. These findings can be used to influence the development of referral protocols to clinical pharmacists for diabetes management and reinforce the importance of interventions such as medication optimization. Innovative services that can incorporate medication optimization, such as pill box filling, could be offered to patients in the future. Here, pharmacists can assist patients in need by optimizing medication regimens, providing education, and reinforcing medication adherence. New pharmacist referral protocols that automatically refer or suggest referral for patients with A1C ≥10% could assist in reaching more patients who may otherwise miss out on this beneficial service. With the increasing healthcare burden in the U.S., primary care will only continue to benefit from clinical pharmacist involvement on healthcare teams. Clinical pharmacists demonstrate clear effectiveness on diabetes outcomes and should be involved in its management when possible. This study supports the continued inclusion of pharmacists on primary healthcare teams, specifically for T2DM management, and further large-scale studies are needed to validate these results. Lastly, future studies should incorporate cost savings data compared to usual care in order to further describe pharmacist impact on the primary healthcare team.

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